Uncommon opportunistic fungi: new nosocomial threats

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During the past two decades opportunistic fungal infections have emerged as important causes of morbidity and mortality in patients with severe underlying illnesses and compromised host defenses. While *Aspergillus* and *Candida* spp. collectively account for the majority of these infections, recent epidemiological trends indicate a shift towards infections by *Aspergillus* spp., non*albicans Candida* spp., as well as previously uncommon opportunistic fungi. Apart from an expanding number of different Zygomycetes, previously uncommon hyaline filamentous fungi (such as *Fusarium* species, *Acremonium* species, *Paecilomyces* species, *Pseudallescheria boydii*, and *Scedosporium prolificans*), dematiaceous filamentous fungi (such as *Bipolaris species, Cladophialophora bantiana, Dactylaria gallopava, Exophiala species, and Alternaria species*) and yeast-like pathogens (such as *Trichosporon* species, *Blastoschizomyces capitatus, Malassezia* species, *Rhodotorula rubra* and others) are increasingly encountered as causing life threatening invasive infections that are often refractory to conventional therapies. On the basis of past and current trends, the spectrum of fungal pathogens will continue to evolve in the settings of an expanding population of immunocompromised hosts, selective antifungal pressures, and shifting conditions in hospitals and the environment. An expanded and refined drug arsenal, further elucidation of pathogenesis and resistance mechanisms, establishment of *in vitro/in vivo* correlations, incorporation of pharmacodynamics, combination- and immunotherapies offer hope for substantial progress in prevention and treatment.

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INTRODUCTION

Opportunistic fungal infections have emerged as important causes of morbidity and mortality in patients with severe underlying illnesses and compromised host defenses [1]. Whereas *Aspergillus* spp. and *Candida* spp. collectively account for the majority of deeply invasive and life-threatening fungal infections, epidemiological trends during the past decade indicate a shift towards infections by *Aspergillus* spp., nonalbicans *Candida* spp., as well as previously uncommon opportunistic fungi [2–7]. The latter include, among others, yeasts such as *Trichosporon beigelii*, filamentous fungi such as *Fusarium* spp., a large variety of dematiaceous moulds, the Zygomycetes as well as endemic dimorphic fungi such as *Penicillium marneffei* [8–11] Conceptually, these emerging fungal infections develop in a dynamic interplay of altered hosts, permissive environmental conditions, and selective antifungal pressures (Figure 1).

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OVERVIEW

The emerging fungal pathogens may be classified as filamentous fungi (moulds) and yeasts; they may be further classified as hyaline or dematiaceous (pigmented). Filamentous fungi also are classified as opportunistic or endemic (dimorphic), and as septated and nonseptated (belonging to the class of Zygomycetes) (Figure 2). Similar to the classic fungal opportunists, the patient population at risk is broad. In general, deficiencies in the number or function

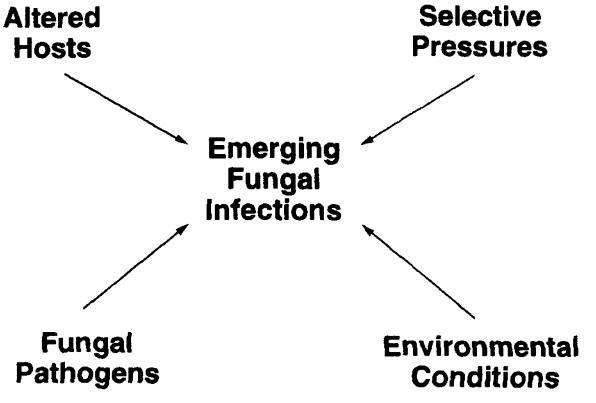

Figure 1 Concepts in emerging fungal infections.

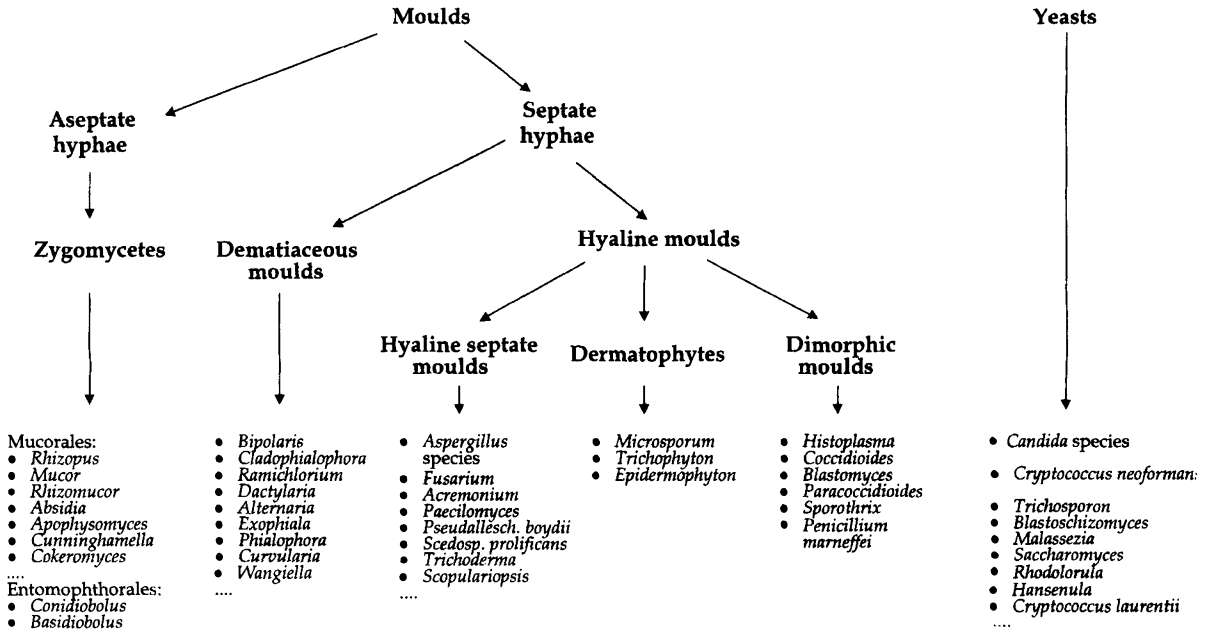

Figure 2 Practical working schema of common and uncommon fungi encountered in immunocompromised patients.

of phagocytic cells are associated with the large variety of opportunistic yeasts and moulds, while deficiencies or imbalance of T-lymphocyte function are linked to the dimorphic moulds as well as to opportunistic moulds in the setting of chronic graft-vs.-host disease and advanced HIV-infection [12]. Important additional nonimmunological factors include the necessary exposure to the organism, pre-existing tissue damage, and, largely limited to yeast-like organisms, the presence of indwelling vascular catheters, colonization of mucocutaneous surfaces, and use of broad-spectrum antibiotics and/or parenteral nutrition [13].

As airborne pathogens, the emerging opportunistic moulds that cause basic disease patterns may be virtually indistinguishable from those of *Aspergillus* spp. Apart from primary invasive infections of the skin and subcutaneous tissues, they affect primarily the sinobronchial tree and have a propensity for dissemination, in particular into the central nervous system. Importantly, some of the hyaline moulds, including *Fusarium* spp., *Paecilomyces* spp., and *Acremonium* spp., express small adventitious structures in tissues that facilitate dissemination and detection of the organism in blood culture systems. Yeast-like pathogens mostly follow the pattern of fungemia and disseminated infection known from *Candida* spp., while infections caused by *Penicillium marneffei* resemble those of disseminated histoplasmosis or cryptococcosis.

Invasive infections by the emerging fungal opportunists are associated with high case fatality rates that appear to even surpass those known from the classic opportunists. Because of the lack of specific clinical, radiographic and histological features and the absence of diagnostic surrogate markers in blood, the diagnosis depends on the identification of the organism by means of culture-based methods. The therapy of most emerging pathogens is not standardized but relies on the use of high-dose amphotericin B (AmB), appropriate surgical measures, and reversal of the underlying impairment of host defenses (see Tables 6 and 7 later in this article). However, some of these organisms are not inherently susceptible to AmB and may require therapies with alternative agents.

This article reviews key emerging opportunistic fungal pathogens that present a risk to immunocompromised patients. Since separate articles in this supplement are devoted to *Candida* spp. and *Aspergillus* spp., the emergence of non-albicans *Candida* spp., azole-resistant *Candida albicans* and unusual *Aspergillus* spp. will not be discussed. *Cryptococcus neoformans* and the endemic moulds of the Americas have been comprehensively reviewed elsewhere [14–25] and are likewise not the subject of this article.

EMERGING FILAMENTOUS FUNGI

Hyaline septated moulds

Fusarium species

Fusarium spp., once considered to cause only infections of the skin, nail, and cornea, are representative of the emerging

group of hyaline moulds which cause sinopulmonary and disseminated infection particularly in granulocytopenic patients undergoing intensive antileukemic chemotherapy or allogeneic hematopoetic stem cell transplantation [26–30]. Indeed, in some cancer centers, *Fusarium* spp. have emerged as the second most common filamentous fungal pathogen after *Aspergillus* [31]. Characterized by canoe-shaped macroconidia, *Fusarium solani, Fusarium oxysporum,* and *Fusarium moniliforme (Fusarium verticilloides)* are the most common species of this ubiquitous mould and plant pathogen [32].

The primary portals of entry of *Fusarium* spp. include lungs, paranasal sinuses, vascular catheters, and breaches in the integrity of the skin, including the periungual regions of the toes. Defenses of the human host depend on pulmonary alveolar macrophages for conidia and neutrophils for hyphal elements. Among immunocompromised hosts, neutropenia appears to be the critical factor, with corticosteroids further adding to the immune-impaired state predisposing to invasive fusariosis. Similarly to *Aspergillus,* this organism is highly angioinvasive and leads to hemorrhagic infarction in pancytopenic hosts [27,28]. *Fusarium* spp. can elaborate potentially lethal mycotoxins in crops; at present, it is unclear whether mycotoxins can be formed within human tissue and contribute to disease [10,32].

The usual initial presentation of invasive fusariosis is persistent fever in a profoundly neutropenic patient. Apart from sinusitis, established infections are characterized by pulmonary infiltrates, metastatic skin lesions and dissemination to multiple tissue sites [27,28]. Perhaps as a result of the occurrence of adventitious sporulation in tissues as mechanism for dissemination [33], *Fusarium* spp. can be recovered in routine blood cultures in 40–60% of cases [28,29]. Histopathological examination of infected tissues, however, is often nonspecific, and on the basis of septate hyaline branching hyphae it is difficult to distinguish *Aspergillus* from other hyaline moulds [34]. Thus, definite diagnosis still relies on the cultural recovery of the organism from infected tissues or the bloodstream. In the near future, however, PCR techniques may detect *Fusarium* spp. earlier in blood cultures or bronchoalveolar lavage samples and simultaneously distinguish it from other filamentous fungi [35].

Responses to treatment of disseminated fusariosis are hampered by marginally effective chemotherapy, particularly in patients with persistent deficiencies in host defenses [27,29]. Overall mortality rates range from 52 to 70%, and are close to 100% in patients who do not recover from neutropenia [26–30]. Fusariosis may be resistant to amphotericin B [36,37] and breakthrough infection during empirical therapy with amphotericin B may occur. One can sometimes achieve stabilization of infection, albeit transiently, with higher doses of amphotericin B in the range of 1.0–1.5 mg/kg or with lipid formulations of amphotericin B using a dose of at least 5 mg/kg per day [38].

In neutropenic patients, rapid recovery from neutropenia is essential for survival. However, while recovery from neutropenia is an essential condition, it may not be a sufficient condition, as the infection may still continue to progress. In other cases, chronic disseminated infection may ensue with consequences similar to those of chronic disseminated candidiasis [26]. Newer therapeutic strategies, however, provide some opportunities for hope: (1) granulocyte or granulocyte/macrophage colony stimulating factors in patients not yet receiving them (2) granulocyte transfusions from GCSF-stimulated donors, and (3) new antifungal agents. While fluconazole and itraconazole are not active against *Fusarium* spp., limited *in vitro* and experimental *in vivo* data and some anecdotal reports suggest that new antifungal triazoles such as posaconazole and voriconazole may exert activity against some *Fusarium* spp. [39–43]. However, in the absence of fungicidal activity of these agents *in vitro* [44–46] and lacking clinical data for treatment in persistently neutropenic hosts, therapy with conventional amphotericin B [47] or one of the lipid formulations of amphotericin B [38] remain the standard initial approach to these devastating infections (Table 1).

Acremonium species

Acremonium species are environmentally widespread hyaline moulds that, when grown in culture, produce small conidia on slender phialides that resemble an early growth of *Fusarium* species. Further incubation, however, does not reveal the characteristic macroconidia observed in *Fusarium* species. Similar to *Fusarium* and *Paecilomyces* spp., *Acremonium* spp. may produce small adventitious unicellular forms (phialoconidia) during infection, which may facilitate dissemination and recovery from the bloodstream [48].

Acremonium causes a spectrum of infections, ranging from mycotic keratitis and mycetoma in normal hosts to fungemia and disseminated infection in immunocompromised patients [48–51]. The lungs and gastrointestinal tract are the apparent portals of entry in immunocompromised patients. Cutaneous lesions may develop during fungemia and disseminated infection. As is true for most emerging pathogens, the optimal therapeutic approach to *Acremonium* infections remains to be determined. In general, *Acremonium* spp. display little susceptibility to current antifungal agents, with best activity seen for amphotericin B [49,51]. However, reported MIC values are comparatively high and clinical responses to amphotericin B therapy in immunocompromised hosts are variable, suggesting that *Acremonium* species may be resistant to conventional dosages of amphotericin B. *Acremonium* infections that are unresponsive to conventional amphotericin B therapy are candidates for treatment with one of the lipid formulations of

Table 1 Chemotherapy of invasive infections by hyaline septated moulds

Fungal disease	Management
Fusarium infections	D-AmB[1.0–1.5 mg/kg/d] or
F. solani	AmB lipid formulations[5 mg/kg/d starting dose]
F. oxysporon	
F. moniliforme	*Second line:*
Acremonium infections	Third-generation antifungal triazoles [investigational]¶
Paecilomyces infections	D-AmB [1.0–1.5 mg/kg/d] or
P. variotii	AmB lipid formulations[5 mg/kg/d starting dose]
P. lilacinus	[first choice for *P. lilacinus*]
	Second line:
	Itraconazole§‡ [200–600 mg/d] [*P. varioti* only]
	Third-generation antifungal triazoles ¶ [investigational]
Pseudallescheria infections	D-AmB [1.0–1.5 mg/kg/d] or
Pseudallescheria boydii	AmB lipid formulations [5 mg/kg/d starting dose]
Scedosporium apiospermum	
	Second line:
	Itraconazole§‡ [200–600 mg/d]
	Third-generation antifungal triazoles ¶ [investigational]
Scedosporium prolificans	No therapy with documented efficacy; consider infections
	high-dose lipid based
	AmB [>5 mg/kg/d] or combination of itraconazole and terbinafine
Trichoderma infections	D-AmB[1.0–1.5 mg/kg/d] or
T. longibrachiatum	AmB lipid formulations[5 mg/kg/d starting dose]
Scopulariopsis infections	*Second line:*
Scopulariopsis brevicaulis	Third-generation antifungal triazoles¶ [investigational]
Deep dermatophytic infections	Fluconazole 400 mg/d or
Trichophyton spp.	Itraconazole 200–400 mg/d or
Microsporon spp.	Terbinafine 250 mg/d
Epidermophyton spp.	

¶Includes posaconazole, ravuconazole, and voriconazole.
‡Monitoring of serum levels recommended (> 0.5 μg/mL [HPLC] or > 2.0 μg/mL [bio-assay] before next dose). Loading dose: 200 mg tid over 3 days. Maximum: 600 mg/d. Intravenous therapy: 200 mg bid over 2 days, followed by 200 mg qd (maximum: 14 days).
§May also be indicated as first line therapy in stable patients with non life-threatening infections.

amphotericin B or, perhaps, one of the investigational antifungal triazoles [39] (Table 1).

Paecilomyces species

Paecilomyces spp. are common environmental hyaline moulds associated with keratitis and soft tissue infections in immunocompetent hosts, but may become the cause of deep infection in immunocompromised patients. The apparent portals of entry for this organism are the respiratory tract, indwelling catheters and the skin [52,53]. The case of the skin as portal of entry is illustrated by an outbreak of disseminated infection due to *Paecilomyces lilacinus*, which occurred on a bone marrow transplantation unit. A medicated skin cream repeatedly obtained from the same jar was the common source and vehicle for transmission of the *P. lilacinus* [54]. Invasive *Paecilomyces* infections may manifest as fungemia, soft tissue infections, pneumonitis and disseminated infection [52–58]. As already noted for *Fusarium* and *Acremonium*, *Paecilomyces* can form adventitious structures within infected tissues that are morphologically consistent with microconidia and can disseminate widely through the bloodstream [33].

While management of localized infections includes surgical resection of infected foci where feasible, the optimal agent for chemotherapy of invasive infections has not been identified. A recent investigation of 52 isolates of 10 *Paecilomyces* species showed high MIC90 for all agents tested. Evaluation of MIC50s indicated overall good activity of amphotericin B and itraconazole, while fluconazole and flucytosine had poor efficacy. However, there were significant susceptibility differences among the different species, and all antifungal agents assayed showed low efficacy against *P. lilacinus* [59]. Promising *in vitro* data have been presented for the new triazoles [39,60]. Nevertheless, correlation to clinical outcomes has not been established for *Paecilomyces* spp., and

therapy must be adjusted to clinical response. In a conservative approach, high-dose amphotericin B is the initial therapeutic intervention for invasive infections in the immunocompromised host; the lipid formulations of amphotericin B are reserved for patients refractory to or intolerant of D-AmB. The role of itraconazole and the investigational triazoles in the primary treatment of invasive infections is unclear, in particular in the setting of persistent neutropenia (Table 1).

Pseudallescheria boydii

Pseudallescheria boydii is a hyaline mould that is characterized microbiologically by terminal annelloconidia and typical cleistothecia in the sexual state (teleomorph form). Some isolates do not display a sexual state (synanamorph form) even under appropriate growth conditions. For such isolates, the designation *Scedosporium apiospermum* is used. It is unknown whether these different growth characteristics *in vitro* are associated with different pathogenic behavior *in vivo*. *P. boydii* may cause pneumonias, sinusitis, CNS infection, endocarditis, disseminated disease, and mycetomas, attendant with severe morbidity and mortality [61–68]. In a review of 31 reported cases of invasive infections, 61% died despite antifungal therapy; among eight patients with localized musculoskeletal soft tissue infection, seven required surgery, and three amputation [61]. In immunosuppressed patients, the principal portal of entry is the respiratory tract. Widespread dissemination from the lungs may ensue to other target organs. Cutaneous nodules may be a harbinger for multifocal dissemination to other organs including the central nervous system. Diagnostic procedures and approaches are similar to those for invasive aspergillosis.

Essential to the treatment of infections due to *P. boydii* and its synanamorph is the correct microbiological diagnosis established by culture [67,69]. Infections caused by these pathogens are often refractory to conventional antifungal therapy, either because of persistently impaired host responses or because of intrinsic microbiological resistance to antifungal compounds [61]. The antifungal activity of amphotericin B *in vitro* is strain dependent and not consistently cidal [70]. Similarly, while itraconazole and particularly voriconazole have very useful inhibitory activity [41,44,46,70–72], this activity appears not to be fungicidal [46,70]. The echinocandins have been shown to have inhibitory *in vitro* activity against *P. boydii* [44,73,74], but antifungal efficacy *in vivo* has not been demonstrated. In the absence of systematic preclinical and clinical data, the optimal treatment for invasive pseudallescheriasis remains to be defined. In the persistently neutropenic patient, high-dose amphotericin B may still be the preferred initial approach with a low threshold for second-line therapy with itraconazole, voriconazole or one of the other still investigational novel broadspectrum triazoles. In less severely immunocompromised patient settings, the antifungal triazoles may represent a valid alternative to amphotericin B. Nevertheless, essential to survival from invasive pseudallescheriasis is the reversal of the underlying cause of immunosuppression and aggressive surgical interventions for amenable lesions. The role of recombinant cytokines and immunomodulation is controversial, but extrapolations from isolated case reports and work with other filamentous fungi may be applicable to this infection [75,76] (Table 1).

Scedosporium prolificans

An increasingly recognized pathogen morphologically related to *P. boydii* is *Scedosporium prolificans* (formerly *Scedosporium inflatum*). This organism has no known sexual state. A rare cause of asymptomatic colonization and localized infections following penetrating trauma in immunocompetent individuals, *S. prolificans* causes rapidly fatal disseminated infections in immunocompromised patients, particularly in those with neutropenia as a result of anticancer treatment or hematopoetic stem cell transplantation [77–79]. As exemplified in one series of 17 cases from Australia, localized disease was managed successfully in immunocompetent patients with local resection, while disseminated disease in immunosuppressed patients was almost universally lethal [77]. Clinical hallmarks of disseminated *S. prolificans* infections are a high rate of antemortem detection of the organism in blood cultures, disseminated hematogenous skin lesions, and signs of CNS-involvement [79]. The respiratory tract appears to be the most frequent portal of entry, but isolated cases indicate that *S. prolificans* may also enter the blood stream through indwelling central venous catheters [78]. The geographic distribution of disseminated *S. prolificans* infections suggests a predilection for Spain and Australia [79]; it is unclear, however, whether there is an ecological background for this apparently particular distribution.

S. prolificans is considered resistant to all current antifungal agents, including the novel antifungal triazoles and the echinocandins [44,71,73,78]. Early recognition and prompt surgical therapy, if possible, is very important. Interferon-γ and GM-CSF can enhance neutrophil superoxide production *in vitro* and may prove useful as immunomodulatory adjunct [80]. Very recently, *in vitro* interaction studies have demonstrated synergistic *in vitro* activity of the combination of itraconazole and terbinafine against 85% of the 20 clinical isolates tested; the minimum inhibitory concentrations of the combination were within the range of achievable plasma levels [81]. Animal models have been developed [82] and should help to clarify whether this or other approaches may lead to improved outcomes from this thus far largely untreatable fungal infection (Table 1).

Trichoderma species

Previously considered a saprophytic organism with low pathogenicity, several centers have recently reported infections

caused principally by *Trichoderma longibrachiatum* [83–85]. Although the genus *Trichoderma* is composed of numerous species, recent molecular studies indicate that virtually all human infections are caused by a single taxonomic 'section' composed of *T. longibrachiatum* [86].

Trichoderma spp. have been reported to cause pulmonary, cerebral, soft tissue and disseminated infections in immunocompromised patients, including those with bone marrow or solid organ transplantation [83–85,87,88]. In tissues, the organisms appear as hyaline moulds that are indistinguishable from other hyalohyphomycetes. Lack of response of infections caused by these organisms to antifungal chemotherapy are consistent with elevated MICs of conventional antifungal agents, including amphotericin B and itraconazole [84,88] in the few strains tested. Recovery from immunosuppression appears to be pivotal to the response of this organism to antifungal chemotherapy. In a manner similar to that of other opportunistic moulds, high-dose amphotericin B is the initial therapeutic intervention for invasive infections; the lipid formulations of amphotericin B are reserved for patients refractory to or intolerant of D-AmB. The investigational triazoles [41,42] may be considered as alternatives to conventional antifungal therapy in patients not responding to these agents (*Table 1*).

Scopulariopsis brevicaulis

Scopulariopsis brevicaulis is a saprophytic hyaline mould that is associated with onychomycosis and occasionally, localized invasive infections following traumatic or surgical injury [89]. In immunocompromised patients, *S. brevicaulis* can cause deeply invasive and disseminated infections with very poor outcome [89–92]. Treatment for disseminated *S. brevicaulis* infections is largely empirical. Based on very limited *in vitro* susceptibility data, approaches to therapy may include amphotericin B or the investigational triazole voriconazole. However, the activity of these agents appears variable [39,72] (Table 1). Terbinafine may be effective in conjunction with surgery for locally invasive infections of skin and perhaps, subcutaneous soft tissues [89,93].

Dermatophytes

Infections caused by dermatophytes (particularly *Microsporum* and *Trichophyton* spp.) in immunocompromised patients may cause locally invasive infection extending into the dermis and causing painful erythematous, nodular or ulcerative lesions, including clinical variations of Majochi's granuloma [94–96]. Because the differential diagnosis of these varied lesions includes disseminated candidiasis, disseminated aspergillosis, fusariosis and ecthyma gangrenosum, biopsy and culture are warranted [96]. Systemic itraconazole, fluconazole or terbinafine are the preferred agents for severe dermatophytosis in immunocompromised patients [97] (Table 1). Terbinafine does not interact with compounds such as cyclosporins that are metabolized through the CYP3A4 pathway [93]. This relative low potential for drug–drug interactions may be useful, particularly in the management of transplant recipients.

Dermatophytes may be readily transmitted throughout a hospital unit [98–100]. Hence, appropriate infection control measures, including hand washing and the use of gloves and gowns, where appropriate, is important in preventing or containing a potential outbreak of nosocomial dermatophytosis.

Dematiaceous septated moulds

The dematiaceous septated moulds represent a diverse group of fungal pathogens, which have in common the presence of melanin-like pigments within the cell wall of their hyphae [101–104]. Among the most prevalent causes of human infection are *Bipolaris* spp., *Cladophialophora bantiana* (formerly, *Xylohypha bantiana; Cladosporium bantianum,* and *Cladosporium trichoides*), *Dactylaria gallopava, Alternaria* spp., *Exophiala* spp., *Phialophora* spp., and *Curvularia* spp. While the dematiaceous moulds typically cause diseases in normal host, such as localized lesions of skin and subcutaneous tissues following a penetrating injury, these pathogens have been increasingly recognized to cause sinusitis, pneumonia, and disseminated infection in immunocompromised patients. Laboratory and clinical studies also demonstrate that these organisms have a high propensity for infection of the central nervous system.

Bipolaris species

Bipolaris spp. are the most common cause of phaeomycotic sinusitis [105–107]. Traditionally, *Bipolaris* sinusitis has been particularly refractory to amphotericin B. Recent findings, however, indicate that itraconazole is active against *Bipolaris* sinusitis, including cases which have been refractory to amphotericin B [108]. The same case series also indicates that itraconazole can be beneficial in treatment of refractory phaeohyphomycosis caused by other dematiaceous moulds, suggesting an important role of itraconazole and, perhaps, the novel triazoles [44,109] in the initial management of these infections (Table 2). Bipolaris also may cause pneumonia, fungemia, and disseminated infection [110–113].

Cladophialophora bantiana

Cladophialophora bantiana (previously termed *Xylohypha bantiana, Cladosporium bantianum,* and *Cladosporium trichoides*) has a high propensity for CNS infection, which is often fatal [114–117]. Notably, patients with CNS infections caused by *Cladophialophora bantiana may* have no apparent immunosuppression, but still succumb to high morbidity and mortality. CNS infection may be best managed with surgical resection

Table 2 Chemotherapy of invasive infections by dematiaceous moulds

Fungal disease	Management
Bipolaris infections	D-AmB [1.0–1.5 mg/kg/d] ± 5-FC # [100 mg/kg/d]
	or
Cladophialophora infections	AmB lipid formulations† [5 mg/kg/d starting dose]
	or
Dactylaria infections	Itraconazole§‡ [200–600 mg/d]
	or
Alternaria infections	Third-generation antifungal triazoles ¶ [investigational]
Curvularia infections	
Wangiella infections	

#Monitoring of serum levels required (< 100 μg/mL; target: 40–60 μg/mL). Dose adjustment with reduced creatinine clearance.
†In patients intolerant to high-dose D-AmB.
§In stable patients with non life-threatening infections.
‡ Monitoring of serum levels recommended (target: > 0.5 μg/mL [HPLC] or > 2.0 μg/mL [bio-assay] before next dose). Loading dose: 200 mg tid over 3 days. Maximum: 600 mg/d. Intravenous therapy: 200 mg bid over 2 days, followed by 200 mg qd (maximum: 14 days).
¶ Includes posaconazole, ravuconazole, and voriconazole.

[114]. The state of encapsulation and inflammation of the CNS lesion appears to be critical in determining outcome, independent of antifungal chemotherapy. Lesions, which were solitary, encapsulated, granulomatous and resectable, were associated with a good prognosis. Those lesions that were multiple, poorly encapsulated, nongranulomatous and multifocal had a poor prognosis [114]. In the absence of a therapeutic standard, the practical approach to therapy is a combination of surgery with systemic antifungal chemotherapy consisting of high-dose amphotericin B. Broad-spectrum antifungal triazoles such as itraconazole or voriconazole have consistent and potent antifungal activity *in vitro* [72,109] that appears to be fungicidal [46] and may provide alternative therapies (Table 2).

Other dematiaceous moulds

Other dematiaceous fungal pathogens are worthy of note. *Ramichloridium obovoideum (R. mackenziei)* is a well-known cause of sinusitis and CNS infection in the Middle East [118,119]. This organism should be considered as an etiological agent in patients referred from this region of the world and who manifest signs of sinusitis or CNS infection. Recent experimental studies indicate that third-generation triazoles may represent an advantage in chemotherapy of these infections [72,120]. Although uncommon, *Dactylaria gallopava* (*Ochroconis gallopava*) causes an aggressive CNS infection in immunocompromised patients [121,122]. Apart from amphotericin B, the organism may be susceptible to itraconazole and voriconazole [109]. Its recovery from any clinical specimen in an immunocompromised host should prompt a careful neurological exam, including diagnostic imaging. Another pathogen, *Wangiella* (*Exophiala*) *dermatitidis*, is recovered in cultures of clinical specimens as a dematiaceous yeast; however, this organism is dimorphic and develops hyphae in human tissue. *W. dermatitidis* can cause catheter-related fungemia [123–125], has a high propensity for CNS infection and is frequently clinically resistant to conventional antifungal agents [103,124]. Recent *in vitro* studies in a few strains, however, show potent and cidal activity of amphotericin B, itraconazole and voriconazole [46] (Table 2).

Zygomycetes

Zygomycetes constitute a class of organisms that are characterized by the presence of sparsely septated, broad and polymorphic hyphae in tissue. They are divided into two orders, i.e. the Mucorales and Entomophthorales [126,127].

The Entomophthorales (*Conidiobolus* and *Basidiobolus* spp. respectively) are true pathogens, causing infections of the nasal submucosa (rhinoenthomophthoromycosis) and subcutaneous infections of extremities and trunk (lobomycosis) predominantly in tropical regions [127,128]. While these organisms are not angioinvasive and rarely disseminate in nonimmunocompromised individuals, occasional cases of disseminated and angioinvasive disease have been described in immunocompromised patients [129], suggesting a possible emerging role for these organisms as opportunists [127].

The majority of cases of zygomycosis (also referred to in the literature as mucormycosis or phycomycosis) are caused by the Mucorales [126,128]. The Mucorales are notorious for causing devastating deeply invasive infections in immunocompromised patients [126,128,130]. While *Rhizopus* spp. is the most commonly implicated organism [126], an expanding spectrum of other Zygomycetes has been reported during the past decade, including but not limited to *Mucor, Rhizomucor, Absidia, Apophysomyces, Cunninghamella,* and *Cokeromyces* [126,130–138]. *Cunninghamella bertholletiae* is associated with

localized or disseminated infection in immunocompromised patients or those receiving desferrioxamine therapy [131–133,136] and may be the cause of breakthrough fungal infections in neutropenic patients receiving itraconazole prophylaxis [138]. In contrast to *R. oryzae,* seldom does *C. bertholletiae* cause rhinocerebral zygomycosis in patients with diabetic ketoacidosis.

In immunocompromised or debilitated hosts, the Zygomycetes have a high propensity for invading blood vessels, for evoking a rapidly deteriorating clinical course refractory to antifungal therapy, and for causing high mortality [126,128]. Zygomycosis may develop in neutropenic states, with corticosteroid therapy, after solid organ and bone marrow transplantation, in patients with uncontrolled diabetic ketoacidosis or with burns, following desferrioxamine therapy for management of iron and aluminum overload states [139], in very-low birth weight infants [137], and in patients with advanced HIV-infection [9].

Infection may develop at various tissue sites and may be classified as follows: (1) rhinocerebral; (2) pulmonary; (3) cutaneous; (4) abdominal-pelvic and gastric; (5) miscellaneous sites; and (6) disseminated disease. Rhinocerebral, pulmonary and disseminated zygomycosis are the most frequently encountered conditions and, at the same time, among the most fulminant fungal infections [126,128]. Rhinocerebral zygomycosis usually begins as an infection of the maxillary or ethmoid sinuses, which progresses to invade the orbit, cavernous sinus and the brain. Hemorrhagic necrosis by blood vessel invasion and thrombosis is typical. A black eschar on the palatine or nasal mucosa and drainage of a black discharge from the eye are characteristic manifestations of tissue infarction [126]. However, these features may also be observed in infections by other filamentous fungi, and are not necessarily pathognomonic for the Zygomycetes [128]. Further clinical symptoms of rhinocerebral zygomycosis may include unilateral headache, ocular irritation, periorbital swelling or numbness, blurred vision, nasal congestion, or epistaxis. The onset of new ocular complaints in a diabetic patient, a patient receiving desferrioxamine, or a pharmacologically immunosuppressed patient should prompt a careful investigation for early rhinocerebral zygomycosis. Rhinocerebral zygomycosis may either progress rapidly, resulting in death within a few days, or it may be a slowly progressive, but relentless process [128]. A detailed radiographic evaluation, including computerized tomographic (CT) scans or magnetic resonance imaging (MRI) is needed to assess the anatomic extent of suspected rhinocerebral zygomycosis and to guide surgical resection of infected tissue.

The presentation of pulmonary zygomycosis in granulocytopenic patients resembles pulmonary aspergillosis with persistent fever and pulmonary infiltrates refractory to antibacterial chemotherapy [130]. The clinical manifestations of pulmonary zygomycosis are a reflection of its pathophysiology: initial bronchopneumonia is followed by pulmonary vascular invasion, thrombosis and hemorrhagic infarction, with potential dissemination to extrapulmonary sites or massive hemorrhage. The sensitivity of cultures from respiratory specimens is low: in a recent series, a culture positive for zygomycetes was typically a preterminal finding in fatal cases [130].

The mainstay of treatment of invasive zygomycosis consists of aggressive surgery for amenable lesions and high-dose amphotericin B (1.0–1.5 mg/kg/day of D-AmB) (Table 3). Triazoles or the echinocandins are inactive as single agents [39,42,46,60,74,140]. Because there are currently no alternatives to amphotericin B, an accurate histological or microbiological diagnosis is essential. Critical to successful outcome of zygomycoses is the reversal of the immunological or metabolic defects that precipitated its development [128]. These strategies include reversal of granulocytopenia, if present, discontinuation of corticosteroids, and correction of metabolic acidosis. The lipid formulations of amphotericin B may reduce the nephrotoxicity of aggressive amphotericin B therapy [141–143]; patients who are neutropenic may benefit from colony stimulating factors to accelerate neutrophil recovery [141].

EMERGING DIMORPHIC MOULDS

Patients with impaired cellular immunity as a result of allogeneic marrow or solid organ transplantation, corticosteroid therapy or HIV infection, who reside or return from endemic areas, are at increased risk for pulmonary and disseminated infections caused by *Coccidioides immitis, Histoplasma capsulatum,* and perhaps, other endemic moulds [13]. By comparison, *Penicillium marneffei* is a newly recognized dimorphic mould that has emerged as a frequent complication in individuals with advanced HIV disease in South-east Asia and China, and has been reported from Europe, Australia and the USA in HIV-infected travellers returning from these areas

Table 3 Chemotherapy of invasive infections by zygomycetes

Mucorales infections	D-AmB [1.0–1.5 mg/kg/d]
Rhizopus spp.	*or*
Mucor spp.	AmB lipid formulation [$\geq$5 mg/kg/d starting dose]
Absidia spp.	
Rhizomucor spp.	
Apophysomyces spp.	
Cunninghamella spp.	
Cokeromyces spp.	
Entomophthorales infections	
Conidiobolus spp.	
Basidiobolus spp.	

[144,145].

While other *Penicillium* spp. are hyaline saprophytic moulds that often contaminate plates in the clinical microbiology laboratory but rarely cause infection [2,146,147], *P. marneffei* is the only dimorphic *Penicillium* species. It is filamentous at room temperature and has a characteristic red diffusible pigment on prolonged incubation. Existing in the filamentous stage at ambient temperature, the conidia from this form in the environment likely enter through the respiratory tract [11] and undergo conversion to an elongated yeast form in tissues and body fluids [148]. *P. marneffei* is a predominantly intracellular pathogen; it divides by binary fission, not by budding *in vivo*. Pulmonary alveolar macrophages and peripheral blood monocytes may be replete with multiple yeast forms with the characteristic binary septate morphology. Cell-mediated immunity appears to play the central role in host defense [149], but cytokine-activated polymorphonuclear leukocytes may contribute additional antifungal activity [150]. Thus, impaired regulation of pulmonary phagocytic functions may be explanatory for the high disease rates in environmentally exposed individuals with advanced HIV infection [11].

The bamboo rat is imputed in the epidemiology of penicilliosis. The bamboo rat, which is not a rat but a member of the genus *Rhizomus* (*Rhizomus prunosis*), has been found to harbor and sometimes succumb to *P. marneffei*. While similar genotypes of *P. marneffei* have been identified in bamboo rats and infected humans [151], this relationship may be coincidental. Indeed, a case control study demonstrated that patients with a recent history of occupational and other exposure to soil, especially during the rainy season, were more likely to present with *P. marneffei* infection. In contrast, history of exposure to or consumption of bamboo rats, the only known nonhuman host of *P. marneffei*, was not a risk factor for infection, suggesting an environmental reservoir of the organism in soil [152].

The most common presenting features of AIDS-associated *P. marneffei* infection in both children and adults include fever, generalized lymphadenopathy, hepatosplenomegaly, pulmonary infiltrate, weight loss or failure to thrive, marked anemia and a generalized papular skin rash reminiscent of mollusca contagiosa [144,145]. In general, the diagnosis is not difficult if the clinical picture is recognized, and it can be readily established by isolation of the organism on conventional media from blood and skin lesions, or, more invasively, from bone marrow aspirates or lymph-node biopsies. A presumptive diagnosis can be made by microscopic examination of appropriately stained smears from skin lesions, bone marrow aspirates, or biopsy material [144,145]. *In vitro* studies show that ketoconazole and itraconazole are the most active agents [153,154]; however, amphotericin B at dosages of 0.5–1.0 mg/kg demonstrated the best response rates for induction therapy in the clinical setting [154,155] (Table 4). Recurrence is common in HIV infection, and life-long maintenance with either itraconazole or ketoconazole [145,156] is indicated and effective in reducing the risk of recurrence [156].

EMERGING YEAST PATHOGENS

Trichosporon species

Trichosporon spp. are pathogenic yeasts that cause life threatening disseminated infection in immunocompromised patients [157–160]. Historically, the mortality associated with disseminated trichosporonosis has been between 60% and 80% [157,159,161], but prognosis has considerably improved as a result of advances in our knowledge regarding diagnosis, treatment and prevention. As characterized by hyphae, pseudohyphae, blastoconidia and arthroconidia, *Trichosporon* species are composed of morphologically, biochemically and genetically distinct subgroups of organisms; these differences become apparent when isolates from deep, superficial and environmental isolates are compared [162,163]. As a consequence, the genus *Trichosporon* has undergone considerable

Table 4 Chemotherapy of invasive infections by dimorphic moulds

Fungal disease	Management
Histoplasmosis	D-AmB [0.5–1.0 mg/kg/d]* Itraconazole§‡ [200–400 mg/d] L-AmB [AmBisome™; 5 mg/kg/d; investigational] †
Blastomycosis and Paracoccidioidomycosis	D-AmB [0.5–1.0 mg/kg/d]* Itraconazole§‡ [200–400 mg/d]
Penicilliosis (*P. marneffei*)	D-AmB [0.5–1.0 mg/kg/d]* Itraconazole§‡ [200–400 mg/d]
Coccidioidomycosis	D-AmB [0.5–1.0 mg/kg/d]* Fluconazoleβ [20[400–800 mg/d]
Sporotrichosis	D-AmB [0.5–1.0 mg/kg/d]* Terbinafine [250 mg/d; investigational]¶

*May be replaced by lipid formulations of AmB in patients who are intolerant to D-AmB, although dosages and antifungal efficacy have not been formally established.

§In stable patients with mild-to-moderate, non-CNS disease, or for long-term maintenance.

‡Monitoring of serum levels recommended (>0.5 μg/mL [HPLC] or >2.0 μg/mL [bio-assay] before next dose). Loading dose: 200 mg tid over 3 days. Maximum: 600 mg/d. Intravenous therapy: 200 mg bid over 2 days, followed by 200 mg qd (maximum: 14 days).

†In patients intolerant or refractory to D-AmB.

βLoading dose: Twice the target dose on the first day of treatment. Dose adjustment may be required with reduced creatinine clearance and high dosages.

¶Cutaneous forms only.

revision in recent years. A proposal has been made for *Trichosporon beigelii* to be revised to five species, including *Trichosporon asahii*, the most common cause of fatal disseminated infection [164]. However, these revisions remain controversial, and although the genus *Trichosporon* includes more than one species, the term *Trichosporon* will be used here for simplicity.

Trichosporon is a common cause of white piedra, which is a simple infection at the distal end of hairshafts. It also has been well characterized as the cause of summer type hypersensitivity in Japan. In immunocompromised patients, particularly those with neutropenia and mucosal disruption caused by cytotoxic chemotherapy, *Trichosporon* causes devastating infection. The portals of entry are the gastrointestinal tract and vascular catheters; however, aspiration may also occur, leading to bronchopneumonia. From these entry sites, the organism can disseminate widely, resulting in a characteristic constellation of findings that include fungemia, renal failure, pulmonary infiltrates, multiple cutaneous lesions and characteristic chorioretinitis; in patients who recover from neutropenia, this process can evolve into a chronic hepatic trichosporonosis [165]. Not uncommonly, acute trichosporonosis presents with a cascade of rapidly evolving skin lesions in a neutropenic patient who is receiving empirical amphotericin B for refractory fever. Laboratory investigations of these organisms have demonstrated that they may be inhibited but not killed by safely achievable levels of amphotericin B [166].

Because the organism belongs to hemibasidiomycetes and, hence, is related to *C. neoformans*, it expresses an antigen that cross-reacts with glucuronoxylomannan (GXM) [167–169]. The GXM-like antigen is expressed in significantly higher concentrations in isolates from patients with fungemia in comparison to environmental sites, and importantly, phagocytosis and microbicidal activity against *Trichosporon* are profoundly suppressed in comparison to those of *C. albicans* [169]. The GXM-like antigen has been shown to be capable of suppressing phagocytosis particularly by the monocyte population, conceivably contributing to the phenomenon of persistent fungemia despite amphotericin B therapy. Of note, *in vitro* treatment of monocytes with GMCSF, MCSF or interferon gamma is able to reverse this immunosuppression and enhance phagocytosis and microbicidal activity of monocytes against *Trichosporon* [170].

A persistently neutropenic rabbit model of gastrointestinal and disseminated trichosporonosis, which simulates the previously mentioned clinical manifestations of this infection, was developed to investigate the pathogenesis and treatment of this refractory infection [171]. Treatment with amphotericin B deoxycholate (1 mg/kg per day) and the multilamellar lipid formulation [172] of amphotericin B (5 mg/kg per day) were unable to clear tissues in comparison with saline-treated controls. This lack of amphotericin B efficacy was consistent with the clinical experience in profoundly neutropenic patients [157,161]. In contrast, antifungal triazoles, such as fluconazole and SCH-39304, resulted in a significant decline in tissue burden [171]. These findings are supported by the results obtained in a murine model of disseminated trichosporonosis, that additionally suggested enhanced antifungal activity *in vivo* of the combination of fluconazole with amphotericin B [161]. Thus, the current data support treatment of disseminated trichosporonosis in persistently neutropenic patients with fluconazole and preferentially GMCSF and possibly, the combination of fluconazole and amphotericin B. Non-neutropenic patients may be treated with fluconazole alone [161,173]. Third-generation triazoles also are active against *Trichosporon* [39,44], whereas the current echinocandins appear inactive [44,140] (Table 5).

Blastoschizomyces capitatus

Blastoschizomyces capitatus (formerly: *Trichosporon capitatum*), although superficially similar to *T. beigelii*, is characterized by the predominant formation of anelloconidia instead of arthroconidia. In neutropenic patients, *B. capitatus* produces a pattern of infection similar to that of *Trichosporon*, but with more frequent CNS involvement. Blood cultures are usually positive during acute disseminated infections. A chronic disseminated form similar to chronic disseminated candidiasis can result in patients who recover from neutropenia [174–177]. The optimal approach to therapy remains to be defined. Similar to *Trichosporon*, *B. capitatus* appears to have decreased susceptibility to amphotericin B [175,178,1174]. Fluconazole and flucytosine appear to be more active *in vitro* [177], but fluconazole-resistant strains have been reported as nosocomial pathogens [179]. Similar to *Trichosporon*, therapy with fluconazole plus amphotericin B and adjuvant immunotherapy [180] may be the most rational strategy at the present time (Table 5).

Malassezia species

Malassezia furfur and *Malassezia pachydermatidis* are lipophilic yeasts that cause tinea versicolor, infectious folliculitis, and catheter-associated fungemia [181–184]. Fungemia caused by *M. furfur* typically develops in the setting of parenteral administration of lipids via central venous catheters [185,186], and *M. pachydermatidis* has been reported as nosocomial infection transmitted from dogs via the hands of health-care workers to preterm neonates [187]. Infection caused by *Malassezia* spp. may present as persistent fever, fungemia, pulmonary infiltrates, and thrombocytopenia. However, the organism seldom disseminates to cause disease

Table 5 Chemotherapy of invasive infections emerging yeast pathogens

Fungal disease	Management
Trichosporon infections	Fluconazoleβ [400–800 mg/d] ± D-AmB [⩾ 1.0 mg/kg/d]*
Blastoschizomyces infections	*Second line:*
	Third generation antifungal triazoles¶ [investigational]
Malassezia infections	D-AmB [0.5–1.0 mg/kg/d] or
	AmB lipid formulations† [5 mg/kg/d starting dose] or
	Fluconazoleβ§ [400–800 mg/d]
Other rare yeast infections	D-AmB [0.5–1.0 mg/kg/d] ± 5-FC #[100 mg/kg/d] or
Saccharomyces cerevisiae	AmB lipid formulations† [5 mg/kg/d starting dose]
Rhodotorula rubra	*Second line:*
Hansenula anomala	Fluconazoleβ§ [400–800 mg/d] or
C. laurentii, and others	Third generation antifungal triazoles¶ [investigational]

βLoading dose: Twice the target dose on the first day of treatment. Dose adjustment may be required with reduced creatinine clearance and high dosages.
*In combination with fluconazole in neutropenic patients.
¶Includes posaconazole, ravuconazole, and voriconazole.
†In patients intolerant to D-AmB.
§Only for identified and *in vitro* susceptible isolates
#Monitoring of serum levels required (<100 μg/mL; target: 40–60 μg/mL). Dose adjustment with reduced creatinine clearance.

in other sites [181–184]. It should be noted that isolated folliculitis in neutropenic patients may simulate the lesions of acute disseminated candidiasis [188]. A direct smear of these lesions, however, will demonstrate characteristic organisms of *M. furfur*.

Laboratory diagnosis is facilitated by the addition of a lipid source such as olive oil [182]. Management includes the discontinuation of parenteral lipids, removal of the vascular catheter, if feasible, and administration of an antifungal azole or amphotericin B [10,13,183,184,189] (Table 5), although *Malassezia* spp. may not be sufficiently susceptible to amphotericin B.

Other emerging yeast pathogens

Invasive infections by other unusual yeast pathogens are more and more frequently encountered in profoundly immunocompromised patients. They may present with a broad range of clinical manifestations and include, among others, *Saccharomyces cerevisiae, Rhodotorula rubra, Hansenula anomala, and Cryptococcus laurentii* [176,190–194]. Of note, a recent report from a single cancer center suggests that invasive non-*Candida* yeast infections collectively carry a significantly worse prognosis than invasive *Candida albicans* infections [176].

In immunocompromised patients, these biologically distinct pathogens can cause fungemia and deeply invasive localized or disseminated infections [2,9,194–197]. The approach to successful management is necessarily individual, but includes antifungal chemotherapy and, intuitively, the removal of potentially colonized intravascular catheters. Most clinical isolates of the four pathogens discussed in this subsection are susceptible to amphotericin B and flucytosine *in vitro*, whereas fluconazole and other triazoles have variable activity [39,193,197–200]. Therefore, high-dose amphotericin B, potentially in combination with flucytosine, appears to be the current first line of antifungal chemotherapy (Table 5).

Table 6 Adjunctive immunoreconstitution in infections by emerging pathogens

Dose-reduction or discontinuation of glucocorticosteroids
Neutropenic patients:
G-or GM-CSF
G-CSF elicited granulocytes [investigational]
Non-neutropenic patients:
GM-CSF or γ-IFN [investigational]

FUTURE DIRECTIONS IN ANTIFUNGAL THERAPY

Infections by previously uncommon fungal opportunists are evolving against a background of a much greater magnitude of invasive candidiasis, especially nonalbicans *Candida* spp., and of invasive pulmonary aspergillosis. In response to this expanding challenge, novel therapeutic and preventive strategies are desperately needed.

For almost four decades, amphotericin B deoxycholate has been the cornerstone of chemotherapy for most invasive fungal infections. The major advantage of this agent is its broad antifungal spectrum and its concentration-dependent fungicidal action against most susceptible fungi [97]. The lipid

Table 7 Adjunctive interventional management of infections by emerging pathogens

Fungal infection and site	Suggested intervention*
Hyaline and dematiaceous moulds	
Pulmonary infections	Potential indications for surgery: *Pulmonary hemorrhage from an amenable lesion* Impeding arosion of a major pulmonary artery Invasion of pericardium or thoracic wall Disease progression despite neutrophil recovery Further intensive chemotherapy or stem cell transplantation Continuing profound immunosuppression
Paranasal sinus infections	Minimally invasive surgery for culture, biopsy and aeration Debridement for progressive invasive disease
Primary skin/soft tissue infections	Excision, if feasible, or debridement and drainage
Fungemia	Removal of indwelling central venous catheters
Infections of all other sites	Individualized approach
Opportunistic yeasts	
Fungemia	Removal of indwelling central venous catheters
Focal lesions	Removal of potentially infected plastic material Debridement/drainage
Meningoencephalitis and increased intracranial pressure	Shunt-placement, if medical therapy is ineffective

*All invasive surgical interventions require a multidisciplinary approach, involving internist, surgeon, radiologist and microbiologist, and often, expert consultation.

formulations of amphotericin B (amphotericin B colloidal dispersion, Amphocil or Amphotec; amphotericin B lipid complex, Abelcet; and the small unilamellar liposomal formulation of amphotericin B, AmBisome) have been shown to be as active as conventional amphotericin B but less nephrotoxic in the treatment of invasive infections by classic fungal opportunists [201,202]. They allow for a safer administration of high daily dosages of amphotericin B and have an important role in the treatment of emerging fungal pathogens that need comparatively higher amphotericin B concentrations for growth inhibition and killing.

Apart from the ongoing search for new compounds and novel targets [203], the third-generation antifungal triazoles (ravuconazole, posaconazole and voriconazole) have increased inhibitory potency against some of the emerging hyaline moulds and, similar to itraconazole, cidal activity against certain dematiaceous moulds [204]. The novel class of echinocandins targets the cell wall of classic fungal opportunists, as well as *Pneumocystis carinii*, by noncompetitive inhibition of 1,3-beta-glucan synthesis [205]. The potential usefulness of the echinocandins as single therapeutics against the emerging fungal opportunists, however, remains to be elucidated.

Because reversal of deficiencies in host defenses is a prerequisite for successful outcome of all opportunistic infections, augmentation of host response in treatment or prevention of invasive fungal infections is being developed through several avenues: direct administration of recombinant cytokines; GCSF-stimulated granulocyte transfusions; harnessing of antimicrobial peptides for protection of mucosal or systemic antifungal therapy; adoptive immunotherapy; and vaccine development, particularly for *C. neoformans* and the dimorphic moulds [206].

CONCLUSIONS

The fungal pathogens that have emerged during the past decade have developed in an expanding population of immunocompromised hosts, new antifungal selective pressures, and shifting environmental conditions. In light of past and present epidemiological trends, invasive fungal infections will probably remain a frequent and important complication in immunocompromised patients. An expanded and refined drug arsenal, elucidation of pathogenesis and resistance mechanisms, establishment of *in vitro/in vivo* correlation, incorporation of pharmacodynamics, combination- and immunotherapies offer hope for further substantial progress in prevention and treatment of previously uncommon opportunistic mycoses.

REFERENCES

1. Bodey GP. The emergence of fungi as major hospital pathogens. *J Hospital Infection* 1988; **11 (Suppl. A)**: 411–26.
2. Anaissie E. Opportunistic mycoses in the immunocompromised host: Experience at a cancer center and review. *Clin Infectious Dis* 1992; **14 (Suppl. 1)**: S43–53.
3. Groll AH, Shah PM, Mentzel C, Schneider M, Just-Nuebling G, Huebner K. Trends in the postmortem epidemiology of invasive fungal infections at a university hospital. *J Infection* 1996; **33**: 23–32.
4. Nguyen MH, Peacock JE Jr, Morris AJ *et al.* The changing face of candidemia: emergence of non-*Candida albicans* species and antifungal resistance. *Am J Med* 1996; **100**: 617–23.
5. Wald A, Leisenring W, Van Burik JA, Bowden RA. Epidemiology of Aspergillus infections in a large cohort of patients undergoing bone marrow transplantation. *J Infectious Dis* 1997; **175**: 1459–66.
6. Viscoli C, Girmenia C, Marinus A *et al.* Candidemia in cancer patients: a prospective, multicenter surveillance study by the Invasive Fungal Infection Group (IFIG) of the European Organization for Research and Treatment of Cancer (EORTC). *Clin Infectious Dis* 1999; **28**: 1071–9.
7. Denning DW, Marinus A, Cohen J *et al.* An EORTC multicentre prospective survey of invasive aspergillosis in haematological patients: diagnosis and therapeutic outcome. EORTC Invasive Fungal Infections Cooperative Group. *J Infection* 1998; **37**: 173–80.
8. Vartivarian SE, Anaissie EJ, Bodey GP. Emerging fungal pathogens in immunocompromised patients: classification, diagnosis, and management. *Clin Infectious Dis* 1993; **17** (Suppl. 2): S487–91.
9. Cunliffe NA, Denning DW. Uncommon invasive mycoses in AIDS. *AIDS* 1995; **9**: 411–20.
10. Perfect JR, Schell WA. The new fungal opportunists are coming. *Clin Infectious Dis* 1996; **22 (Suppl. 2)**: S112–8.
11. Duong TA. Infection due to *Penicillium marneffei*, an emerging pathogen: review of 155 reported cases. *Clin Infectious Dis* 1996; **23**: 125–30.
12. Romani L, Howard DH. Mechanisms of resistance to fungal infections. *Current Opinion Immunol* 1995; **7**: 517–23.
13. Walsh TJ, Hiemenz JW, Anaissie E. Recent progress and current problems in treatment of invasive fungal infections in neutropenic patients. *Infectious Dis Clin North Am* 1996; **10**: 365–400.
14. White MH, Armstrong D. Cryptococcosis. *Infectious Dis Clin North Am* 1994; **8**: 383–98.
15. Hajjeh RA. Disseminated histoplasmosis in persons infected with human immunodeficiency virus. *Clin Infectious Dis* 1995; **21 (Suppl. 1)**: S108–10.
16. Suzaki A, Kimura M, Kimura S, Shimada K, Miyaji M, Kaufman L. An outbreak of acute pulmonary histoplasmosis among travelers to a bat-inhabited cave in Brazil. *Kansenshogaku Zasshi* 1995; **69**: 444–9.
17. Bradsher RW. Histoplasmosis and blastomycosis. *Clin Infectious Dis* 1996; **22 (Suppl. 2)**: S102–11.
18. Aberg JA, Powderly WG. Cryptococcosis. *Adv Pharmacol* 1997; **37**: 215–51.
19. Galgiani JN. Coccidioidomycosis. *Current Clin Topics Infectious Diseases* 1997; **17**: 188–204.
20. Schneider E, Hajjeh RA, Spiegel RA *et al.* A coccidioidomycosis outbreak following the Northridge, Calif, earthquake. *J Am Med Assoc* 1997; **277**: 904–8.
21. Wheat J. Histoplasmosis. Experience during outbreaks in Indianapolis and review of the literature. *Medicine (Baltimore)* 1997; **76**: 339–54.
22. Muller FM, Groll AH, Walsh TJ. Current approaches to diagnosis and treatment of fungal infections in children infected with human immunodeficiency virus. *Eur J Pediatrics* 1999; **158**: 187–99.
23. Lortholary O, Denning DW, Dupont B. Endemic mycoses: a treatment update. *J Antimicrob Chemotherapy* 1999; **43**: 321–31.
24. Cairns L, Blythe D, Kao A *et al.* Outbreak of coccidioidomycosis in Washington state residents returning from Mexico. *Clin Infectious Dis* 2000; **30**: 61–64
25. Harrison TS. *Cryptococcus neoformans* and cryptococcosis. *J Infection* 2000; **41**: 12–7.
26. Gamis AS, Gudnason T, Giebink GS, Ramsay NK. Disseminated infection with Fusarium in recipients of bone marrow transplants. *Rev Infectious Dis* 1991; **13**: 1077–88.
27. Martino P, Gastaldi R, Raccah R, Girmenia C. Clinical patterns of *Fusarium* infections in immunocompromised patients. *J Infection Suppl* 1994; **1**: 7–15.
28. Boutati EI, Anaissie EJ. *Fusarium*, a significant emerging pathogen in patients with hematologic malignancy: ten years' experience at a cancer center and implications for management. *Blood* 1997; **90**: 999–1008.
29. Hennequin C, Lavarde V, Poirot JL *et al.* Invasive Fusarium infections: a retrospective survey of 31 cases. The French 'Groupe d'Etudes des Mycoses Opportunistes' GEMO. *J Med Vet Mycol* 1997; **35**: 107–14.
30. Musa MO, Al Eisa A, Halim M *et al.* The spectrum of Fusarium infection in immunocompromised patients with haematological malignancies and in non-immunocompromised patients: a single institution experience over 10 years. *Br J Hematol* 2000; **108**: 544–8.
31. Anaissie E, Kantarjian H, Ro J *et al.* The emerging role of *Fusarium* infections in patients with cancer. *Medicine (Baltimore)* 1988; **67**: 77–83.
32. Nelson PE, Dignani MC. Anaissie. Taxonomy, biology, and clinical aspects of *Fusarium* species. *Clin Microbiol Rev* 1994; **7**: 479–504.
33. Liu K, Howell DN, Perfect JR, Schell WA. Morphologic criteria for the preliminary identification of *Fusarium*, *Paecilomyces*, and *Acremonium* species by histopathology. *Am J Clin Pathol* 1998; **109**: 45–54.
34. Schwartz J. The diagnosis of deep mycoses by morphological methods. *Human Pathol* 1982; **13**: 519–33.
35. Walsh TJ, Francesconi A, Kasai M, Chanock S. Polymerase chain reaction and single strand conformational polymorphism (SSCP) for recognition of medically important opportunistic fungi. *J Clin Microbiol* 1995; **33**: 3216–20.
36. Reuben A, Anaissie E, Nelson PE *et al.* Antifungal susceptibility of 44 clinical isolates of *Fusarium* species determined by.
37. Anaissie EJ, Hachem R, Legrand C, Legenne P, Nelson P, Bodey GP. Lack of activity of amphotericin B in systemic murine fusarial infection. *J Infectious Dis* 1992; **165**: 1155–7.
38. Walsh TJ, Hiemenz JW, Seibel N *et al.* lipid complex in patients with invasive fungal infections: analysis of safety and efficacy in 556 cases. *Clin Infectious Dis* 1998; **26**: 1383–96.
39. Wildfeuer A, Seidl HP, Paule I, Haberreiter A. *In vitro* activity of voriconazole against yeasts, moulds and dermatophytes in comparison with fluconazole, amphotericin B and griseofulvin. *Arzneimittelforschung* 1997; **47**: 1257–63.
40. McGinnis MR, Pasarell L, Sutton DA, Fothergill AW, Cooper Jr CR, Rinaldi MG. *In vitro* activity of voriconazole against selected fungi. *Med Mycol* 1998; **36**: 239–42.
41. Marco F, Pfaller MA, Messer SA, Jones RN. Antifungal activity of a new triazole, voriconazole (UK-109,496), compared with three other antifungal agents tested against clinical isolates of filamentous fungi. *Med Mycol* 1998; **36**: 433–6.
42. Marco F, Pfaller MA, Messer SA, Jones RN. In vitro activity of a new triazole antifungal agent, Sch 56592, against clinical isolates of filamentous fungi. *Mycopathologia* 1998; **141**: 73–7.
43. Lozano-Chiu M, Arikan S, Paetznick VL, Anaissie EJ, Loebenberg D, Rex JH. Treatment of murine fusariosis with SCH 56592. *Antimicrobial Agents Chemotherapy* 1999; **43**: 589–91.
44. Espinel-Ingroff A. Comparison of In vitro activities of the new triazole SCH56592 and the echinocandins MK-0991 (L-743,872) and LY303366 against opportunistic filamentous and dimorphic fungi and yeasts. *J Clin Microbiol* 1998; **36**: 2950–6.

45. Clancy CJ, Nguyen MH. In vitro efficacy and fungicidal activity of voriconazole against Aspergillus and Fusarium species. *Eur J Clin Microbiol Infectious Dis* 1998; **17**: 573–5.
46. Johnson EM, Szekely A, Warnock DW. In-vitro activity of voriconazole, itraconazole and amphotericin B against filamentous fungi. *J Antimicrobial Chemotherapy* 1998; **42**: 741–5.
47. Merz W, Karp J, Hoagland M *et al.* Diagnosis and successful treatment of fusariosis in the compromised host. *J Infectious Dis* 1988; **158**: 1046–55.
48. Schell WA, Perfect JR. Fatal disseminated *Acremonium strictum* infection in a neutropenic host. *J Clin Microbiol* 1996; **34**: 1333–6.
49. Fincher RM, Fisher JF, Lovell RD, Newman CL, Espinel-Ingroff A, Shadomy HJ. Infection due to the fungus Acremonium (cephalosporium). *Medicine (Baltimore)* 1991; **70**: 398–409.
50. Roilides E, Bibashi E, Acritidou E *et al. Acremonium* fungemia in two immunocompromised children. *Pediatric Infectious Dis J* 1995; **14**: 548–50.
51. Guarro J, Gams W, Pujol I, Gene J. *Acremonium* species: new emerging fungal opportunists—in vitro antifungal susceptibilities and review. *Clin Infectious Dis* 1997; **25**: 1222–9.
52. Castro LG, Salebian A, Sotto MN. Hyalohyphomycosis by *Paecilomyces lilacinus* in a renal transplant patient and a review of human *Paecilomyces* species infections. *J Med Vet Mycol* 1990; **28**: 15–26.
53. Chan-Tack KM, Thio CL, Miller NS, Karp CL, Ho C, Merz WG. *Paecilomyces lilacinus* fungemia in an adult marrow transplant recipient. *Med Mycol* 1999; **37**: 57–60.
54. Orth B, Frei R, Itin PH *et al.* Outbreak of invasive mycoses caused by *Paecilomyces lilacinus* from a contaminated skin lotion. *Ann Intern Med* 1996; **125**: 799–806.
55. Tan TQ, Ogden AK, Tillman J, Demmler GJ, Rinaldi MG. *Paecilomyces lilacinus* catheter-related fungemia in an immunocompromised pediatric patient. *J Clin Microbiol* 1992; **30**: 2479–83.
56. Naiad J, Singh SM. Hyalohyphomycosis caused by *Paecilomyces variotii*: a case report, animal pathogenicity and 'in vitro' sensitivity. *Antonie Van Leeuwenhoek* 1992; **62**: 225–30.
57. Williamson PR, Kwon-Chung KJ, Gallin JI. Successful treatment of *Paecilomyces variotii* infection in a patient with chronic granulomatous disease and a review of Paecilomyces species infections. *Clin Infectious Dis* 1992; **14**: 1023–6.
58. Shing MM, Ip M, Li CK, Chik KW, Yuen PM. *Paecilomyces variotii* fungemia in a bone marrow transplant patient. *Bone Marrow Transplantation* 1996; **17**: 281–3.
59. Aguilar C, Pujol I, Sala J, Guarro J. Antifungal susceptibilities of Paecilomyces species. *Antimicrob Agents Chemotherapy* 1998; **42**: 1601–4.
60. Fung-Tome JC, Huczko E, Minassian B, Bonner DP. In vitro activity of a new oral triazole, BMS-207147 (ER-30346). *Antimicrob Agents Chemotherapy* 1998; **42**: 313–8.
61. Travis LB, Roberts GD, Wilson WR. Clinical significance of *Pseudallescheria boydii*: A review of 10 years' experience. *Mayo Clinic Proc* 1985; **60**: 531–7.
62. Berenguer J, Diaz-Mediavilla J, Urra D, Munoz P. Central nervous system infection caused by *Pseudallescheria boydii*: Case report and review. *Rev Infectious Dis* 1990; **11**: 890–6.
63. Kershaw P, Freeman R, Templeton D *et al. Pseudallescheria boydii* infection of the central nervous system. *Arch Neurol* 1990; **47**: 468–72.
64. Patterson TF, Andriole VT, Zervos MJ, Therasse D, Kauffman CA. The epidemiology of pseudallescheriasis complicating transplantation: nosocomial and community-acquired infection. *Mycoses* 1990; **33**: 297–302.
65. Grigg AP, Phillips P, Durham S, Shepherd JD. Recurrent *Pseudallescheria boydii* sinusitis in acute leukemia. *Scand J Infectious Dis* 1993; **25**: 263–7.
66. Singh N, Chang FY, Gayowski T, Marino IR. Infections due to dermatiaceous fungi in organ transplant recipients: case report and review. *Clin Infectious Dis* 1997; **24**: 369–74.
67. Tadros TS, Workowski KA, Siegel RJ, Hunter S, Schwartz DA. Pathology of hyalohyphomycosis caused by *Scedosporium apiospermum* (*Pseudallescheria boydii*): an emerging mycosis. *Human Pathol* 1998; **29**: 1266–72.
68. Munoz P, Marin M, Tornero P, Martin Rabadan P, Rodriguez-Creixems M, Bouza E. Successful outcome of *Scedosporium apiospermum* disseminated infection treated with voriconazole in a patient receiving corticosteroid therapy. *Clin Infectious Dis* 2000; **31**: 1499–501.
69. Lopez FA, Crowley RS, Wastila L, Valantine HA, Remington JS. *Scedosporium apiospermum* (*Pseudallescheria boydii*) infection in a heart transplant recipient: a case of mistaken identity. *J Heart Lung Transplant* 1998; **17**: 321–4.
70. Walsh TJ, Peter J, McGough DA, Fothergill AW, Rinaldi MG, Pizzo PA. Activity of amphotericin B and antifungal azoles alone and in combination against *Pseudallescheria boydii*. *Antimicrob Agents Chemotherapy* 1995; **39**: 1361–4.
71. Cuenca-Estrella M, Ruiz-Diez B, Martinez-Suarez JV, Monzon A, Rodriguez-Tudela JL. Comparative in-vitro activity of voriconazole (UK-109,496) and six other antifungal agents against clinical isolates of *Scedosporium prolificans* and *Scedosporium apiospermum*. *J Antimicrobial Chemotherapy* 1999; **43**: 149–51.
72. Radford SA, Johnson EM, Warnock DW. In vitro studies of activity of voriconazole (UK-109,496), a new triazole antifungalagent, against emerging and less-common mold pathogens. *Antimicrob Agents Chemotherapy* 1997; **41**: 841–3.
73. Del Poeta M, Schell WA, Perfect JR. In vitro antifungal activity of pneumocandin L-743,872 against a variety of clinically important molds. *Antimicrobial Agents Chemotherapy* 1997; **41**: 1835–6.
74. Pfaller MA, Marco F, Messer SA, Jones RN. In vitro activity of two echinocandin derivatives, LY303366 and MK-0991 (L-743,792), against clinical isolates of Aspergillus, Fusarium, Rhizopus, and other filamentous fungi. *Diagnostic Microbiol Infectious Dis* 1998; **30**: 251–5.
75. Phillips P, Forbes JC, Speert DP. Disseminated infection with *Pseudallescheria boydii* in a patient with chronic granulomatous disease: response to gamma-interferon plus antifungal chemotherapy. *Pediatric Infectious Dis J* 1991; **10**: 536–9.
76. Roilides E, Uhlig K, Venzon D, Pizzo PA, Walsh TJ. Enhancement of oxidative response and damage caused by neutrophils to *Aspergillus fumigatus* hyphae by granulocyte colony stimulating factor and interferon-gamma. *Infection Immunity* 1993; **61**: 1185–93.
77. Wood GM, McCormack JG, Muir DB *et al.* Clinical features of human infection with *Scedosporium inflatum*. *Clin Infectious Dis* 1992; **14**: 1027–33.
78. Berenguer J, Rodriguez-Tudela JL, Richard C *et al.* Deep infections caused by *Scedosporium prolificans*. A report on 16 cases in Spain and a review of the literature. *Scedosporium prolificans Spanish Study Group Med (Baltimore)* 1997; **76**: 256–65.
79. Maertens J, Lagrou K, Deweerdt H *et al.* Disseminated infection by *Scedosporium prolificans*: an emerging fatality among haematology patients. Case report and review. *Ann Hematol* 2000; **79**: 340–4.
80. Gil-Lamaignere C, Rodriguez-Tudela L, Roilides E. Human phagocytic cell responses to *Scedosporium prolificans* hyphae. In *39th International Conference on Antimicrobial Agents and Chemotherapy*, abstract 1617, 390. American Society for Microbiology, Washington, DC, 1999.
81. Meletiadis J, Mouton JW, Rodriguez-Tudela JL, Meis JF, Verweij PE. In vitro interaction of terbinafine with itraconazole against clinical isolates of *Scedosporium prolificans*. *Antimicrobial Agents Chemotherapy* 2000; **44**: 470–2.
82. Meletiadis J, Curfs J, Meis JFG, Verweij PE. An animal model for invasive infections caused by *Scedosporium prolificans*. In *40th International Conference on Antimicrobial Agents and Chemotherapy*, abstract 1670, 384. American Society for Microbiology, Washington, DC, 2000.

83. Gautheret A, Dromer F, Bourhis JH, Andremont A. *Trichoderma pseudokoningii* as a cause of fatal infection in a bone marrow transplant recipient. *Clin Infectious Dis* 1995; **20**: 1063–4.
84. Munoz FM, Demmler GJ, Travis WR, Ogden AK, Rossmann SN, Rinaldi MG. *Trichoderma longibrachiatum* infection in a pediatric patient with aplastic anemia. *J Clin Microbiol* 1997; **35**: 499–503.
85. Richter S, Cormican MG, Pfaller MA *et al.* Fatal disseminated *Trichoderma longibrachiatum* infection in an adult bone marrow transplant patient: species identification and review of the literature. *J Clin Microbiol* 1999; **37**: 1154–60.
86. Kuhls K, Lieckfeldt E, Börner T, Gueho E. Molecular identification of human pathogenic *Trichoderma* isolates of *Trichoderma longibrachiatum* and *Trichoderma citroinviride*. *Med Mycol* 1999; **37**: 25–33.
87. Jacobs F, Byl B, Bourgeois N *et al. Trichoderma viride* infection in a liver transplant recipient. *Mycoses* 1992; **35**: 301–3.
88. Guarro J, Antolin-Ayala MI, Gene J, Gutierrez-Calzada J, Nieves-Diez C. Ortoneda M. Fatal case of Trichoderma harzianum infection in a renal transplant recipient. *J Clin Microbiol* 1999; **37**: 3751–5.
89. Sellier P, Monsuez JJ, Lacroix C *et al.* Recurrent subcutaneous infection due to *Scopulariopsis brevicaulis* in a liver transplant recipient. *Clin Infectious Dis* 2000; **30**: 820–3.
90. Neglia JP, Hurd DD, Ferrieri P, Snover DC. Invasive Scopulariopsis in the immunocompromised host. *Am J Med* 1987; **83**: 1163–6.
91. Phillips P, Wood WS, Phillips G, Rinaldi MG. Invasive hyalohyphomycosis caused by *Scopulariopsis brevicaulis* in a patient undergoing allogeneic bone marrow transplant. *Diagnostic Microbiol Infectious Dis* 1989; **12**: 429–32.
92. Kriesel JD, Adderson EE, Gooch WM 3rd, Pavia AT. Invasive sinonasal disease due to Scopulariopsis candida: case report and review of scopulariopsosis. *Clin Infectious Dis* 1994; **19**: 317–9.
93. Balfour JA, Faulds D. Terbinafine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in superficial mycoses. *Drugs* 1992; **43**: 259–84.
94. Engelhard D, Or R, Naparstek E, Leibovici V. Treatment with itraconazole of widespread tinea corporis due to *Trichophyton rubrum* in a bone marrow transplant recipient. *Bone Marrow Transplant* 1988; **3**: 517–9.
95. Grossman ME, Pappert AS, Garzon MC, Silvers DN. Invasive *Trichophyton rubrum* infection in the immunocompromised host: report of three cases. *J Am Acad Dermatol* 1995; **33**: 315–8.
96. King D, Cheever LW, Hood A, Horn TD, Rinaldi MG, Merz WG. Primary invasive cutaneous *Microsporum canis* infections in immunocompromised patients. *J Clin Microbiol* 1996; **34**: 460–2.
97. Groll A, Walsh TJ. Pharmacology of antifungal compounds. *Adv Pharmacol* 1998; **44**: 343–500.
98. Arnow PM, Houchins SG, Pugliese G. An outbreak of tinea corporis in hospital personnel caused by a patient with *Trichophyton tonsurans* infection. *Pediatric Infectious Dis J* 1991; **10**: 355–9.
99. Lewis SM, Lewis BG. Nosocomial transmission of *Trichophyton tonsurans tinea corporis* in a rehabilitation hospital. *Infection Control Hospital Epidemiol* 1997; **18**: 322–5.
100. Snider R, Landers S, Levy ML. The ringworm riddle: an outbreak of *Microsporum canis* in the nursery. *Pediatric Infectious Dis J* 1993; **12**: 145–8.
101. Matsumoto T, Ajello L, Matsuda T, Szaniszlo PJ, Walsh TJ. Developments in phaeohyphomycosis and hyalohyphomycosis. *J Med Vet Mycol* 1994; **32 (Suppl. 1)**: 329–49.
102. Fothergill AW. Identification of dematiaceous fungi and their role in human disease. *Clin Infectious Dis* 1996; **22 (Suppl. 2)**: S179–84.
103. Rinaldi MG. Phaeohyphomycosis. *Dermatol Clinics* 1996; **14**: 147–53.
104. De Hoog GS. Significance of fungal evolution for the understanding of their pathogenicity, illustrated with agents of phaeohyphomycosis. *Mycoses* 1997; **40 (Suppl. 2)**: 5–8.
105. Antoine GA, Raternik MH. *Bipolaris*: a serious new fungal pathogen of the paranasal sinus. *Otolaryngol Head Neck Surg* 1989; **100**: 158–62.
106. Maskin SL, Fetchick RJ, Leone CR Jr, Sharkey PK, Rinaldi MG. *Bipolaris hawaiiensis*-caused phaeomycotic orbitopathy. A devastating fungal sinusitis in an apparently immunocompetent host. *Ophthalmology* 1989; **96**: 175–9.
107. Jacobson M, Galetta SL, Atlas SW, Curtis MT, Wulc AW. *Bipolaris*-induced orbital cellulitis. *J Clin Neuroophthalmol* 1992; **12**: 250–6.
108. Sharkey K, Graybill JR, Rinaldi MG *et al.* Itraconazole treatment of phaeohyphomycosis. *J Am Acad Dermatol* 1990; **23**: 577–86.
109. McGinnis MR, Pasarell L. In vitro testing of susceptibilities of filamentous ascomycetes to voriconazole, itraconazole, and amphotericin B, with consideration of phylogenetic implications. *J Clin Microbiol* 1998; **36**: 2353–5.
110. Adam RD, Paquin ML, Petersen EA, Saubelle MA, Rinaldi MG. Phaeohyphomycosis caused by the fungal genera *Bipolaris* and *Exserohilum*. A report of nine cases and review of the literature. *Medicine (Baltimore)* 1986; **65**: 203–17.
111. Morton SJ, Midthun K, Merz WG. Granulomatous encephalitis caused by *Bipolaris hawaiiensis*. *Arch Pathol Laboratory Med* 1986; **110**: 1183–5.
112. Flanagan KL, Bryceson AD. Disseminated infection due to *Bipolaris australiensis* in a young immunocompetent man: case report and review. *Clin Infectious Dis* 1997; **25**: 311–3.
113. Pauzner R, Goldschmied-Reouven A, Hay I *et al.* Phaeohyphomycosis following cardiac surgery: case report and review of serious infection due to Bipolaris and Exserohilum species. *Clin Infectious Dis* 1997; **25**: 921–3.
114. Dixon DM, Walsh TJ, Merz WG, McGinnis MR. Human central nervous system infections due to *Xylohypha bantiana (Cladosporium trichoides). Rev Infectious Dis* 1989; **11**: 515–25.
115. Aldape KD, Fox HS, Roberts JP, Ascher NL *et al. Cladosporium trichoides* cerebral phaeohyphomycosis in a liver transplant recipient. Report of a case. *Am J Clin Pathol* 1991; **95**: 499–502.
116. Goel A, Satoskar A, Desai AP, Pandya SK. Brain abscess caused by *Cladosporium trichoides*. *Br J Neurosurgery* 1992; **6**: 591–3.
117. Emmens RK, Richardson D, Thomas W *et al.* Necrotizing cerebritis in an allogeneic bone marrow transplant recipient due to *Cladophialophora bantiana*. *J Clin Microbiol* 1996; **34**: 1330–2.
118. Naim-ur-Rahman, Mahgoub ES, Chagla AH. Fatal brain abscesses caused by *Ramichloridium obovoideum*: report of three cases. *Acta Neurochirurgica (Wien)* 1988; **93**: 92–5.
119. Sutton DA, Slifkin M, Yakulis R, Rinaldi MG. U.S. case report of cerebral phaeohyphomycosis caused by *Ramichloridium obovoideum* (R. mackenziei): criteria for identification, therapy, and review of other known dematiaceous neurotropic taxa. *J Clin Microbiol* 1998; **36**: 708–15.
120. Al-Abdely HM, Najvar L, Bocanegra R *et al.* 56592, amphotericin B, or itraconazole therapy of experimental murine cerebral phaeohyphomycosis due to *Ramichloridium obovoideum* ('*Ramichloridium mackenziei*'). *Antimicrobial Agents Chemotherapy* 2000; **44**: 1159–62.
121. Vukmir RB, Kusne S, Linden P *et al.* Successful therapy for cerebral phaeohyphomycosis due to *Dactylaria gallopava* in a liver transplant recipient. *Clin Infectious Dis* 1994; **19**: 714–9.
122. Kralovic SM, Rhodes JC. Phaeohyphomycosis caused by *Dactylaria* (human dactylariosis): report of a case with review of the literature. *J Infection* 1995; **31**: 107–13.
123. Kabel PJ, Illy KE, Holl RA, Buiting AG, Wintermans RG. Nosocomial intravascular infection with *Exophiala dermatitidis*. *Lancet* 1994; **344**: 1167–8.
124. Nachman S, Alpan O, Malowitz R, Spitzer ED. Catheter-associated fungemia due to *Wangiella (Exophiala) dermatitidis*. *J Clin Microbiol* 1996; **34**: 1011–3.
125. Ajanee N, Alam M, Holmberg K, Khan J. Brain abscess caused by *Wangiella dermatitidis:* case report. *Clin Infectious Dis* 1996; **23**: 197–198.

126. Sugar AM. Mucormycosis. *Clin Infectious Dis* 1992; **14 (Suppl. 1)**: S126–9.
127. Ribes JA, Vanover-Sams CL, Baker DJ. Zygomycetes in human disease. *Clin Microbiol Rev* 2000; **13**: 236–301.
128. Irwin RG, Rinaldi MG, Walsh TJ. Zygomycosis of the respiratory tract. In: Sarosi G, Davies S, eds. *Fungal Diseases of the Lung*, 3rd edn. Lippincott Williams & Wilkins, Philadelphia, PA, 2000: 163–86.
129. Walsh TJ, Renshaw G, Andrews J *et al.* Invasive zygomycosis due to *Conidiobolus incongruus*. *Clin Infectious Dis* 1994; **19**: 423–30.
130. Kontoyiannis DP, Wessel VC, Bodey GP, Rolston KV. Zygomycosis in the 1990s in a tertiary-care cancer center. *Clin Infectious Dis* 2000; **30**: 851–6.
131. Kolbeck PC, Makhoul RG, Bollinger RR, Sanfilippo F. Widely disseminated *Cunninghamella* mucormycosis in an adult renal transplant patient: Case report and review of the literature. *Am J Clin Pathol* 1985; **83**: 747.
132. Nimmo GR, Whiting RF, Strong RW. Disseminated mucormycosis due to *Cunninghamella bertholletiae* in a liver transplant recipient. *Postgraduate Med J* 1988; **64**: 82–4.
133. Rex JH, Ginsberg AM, Fries LF, Pass HI, Kwon-Chung KJ. *Cunninghamella bertholletiae* infection associated with deferoxamine therapy. *Rev Infectious Dis* 1988; **10**: 1187–94.
134. Cooter RD, Lim IS, Ellis DH, Leitch IO. Burn wound zygomycosis caused by *Apophysomyces elegans*. *J Clin Microbiol* 1990; **28**: 2151–3.
135. Fingeroth JD, Roth RS, Talcott JA, Rinaldi M. Zygomycosis due to *Mucor circinelloides* in a neutropenic patient receiving chemotherapy for acute myelogenous leukemia. *Clin Infectious Dis* 1994; **19**: 135–7.
136. Kontoyianis DP, Vartivarian S, Anaissie EJ, Samonis G, Bodey GP, Rinaldi M. Infections due to *Cunninghamella bertholletiae* in patients with cancer: report of three cases and review. *Clin Infectious Dis* 1994; **18**: 925–8.
137. Robertson AF, Joshi VV, Ellison DA, Cedars JC. Zygomycosis in neonates. *Pediatric Infectious Dis J* 1997; **16**: 812–5.
138. Rickerts V, Bohme A, Viertel A *et al.* Cluster of pulmonary infections caused by *cunninghamella bertholletiae* in immunocompromised patients. *Clin Infectious Dis* 2000; **31**: 910–3.
139. Daly AL, Velazquez LA, Bradley SF, Kauffman CA. Mucormycosis association with deferoxamine therapy. *Am J Med* 1989; **87**: 468–71.
140. Tawara S, Ikeda F, Maki K *et al.* In vitro activities of a new lipopeptide antifungal agent, FK463, against a variety of clinically important fungi. *Antimicrobial Agents Chemotherapy* 2000; **44**: 57–62.
141. Gonzalez CE, Couriel DR, Walsh TJ. Successful treatment of disseminated zygomycosis in a neutropenic patient with amphotericin B lipid complex and granulocyte colony stimulating factor. *Clin Infectious Dis* 1997; **24**: 192–6.
142. Baraia J, Munoz P, Bernaldo de Quiros JC, Bouza E. Cutaneous mucormycosis in a heart transplant patient associated with a peripheral catheter. *Eur J Clin Microbiol Infectious Dis* 1995; **14**: 813–5.
143. Fortun J, Cobo J, Canal J, Martinez-San Millan J. Post-traumatic cranial mucormycosis in an immunocompetent patient. *J Oral Maxillofacial Surg* 1995; **53**: 1099–102.
144. Supparatpinyo K, Khamwan C, Baosoung V, Nelson KE, Sirisanthana T. Disseminated *Penicillium marneffei* infection in Southeast Asia. *Lancet* 1994; **344**: 110–3.
145. Sirisanthana V, Sirisanthana T. Disseminated *Penicillium marneffei* infection in human immunodeficiency virus-infected children. *Pediatric Infectious Dis J* 1995; **14**: 935–40.
146. de la Camara R, Pinilla I, Munoz E, Buendia B, Steegmann JL, Fernandez-Ranada JM. *Penicillium brevicompactum* as the cause of a necrotic lung ball in an allogeneic bone marrow transplant recipient. *Bone Marrow Transplant* 1996; **18**: 1189–93.
147. Mok T, Koehler AP, Yu MY, Ellis DH, Johnson PJ, Wickham NW. Fatal *Penicillium citrinum* pneumonia with pericarditis in a patient with acute leukemia. *J Clin Microbiol* 1997; **35**: 2654–6.
148. Cooper CR Jr, Haycocks NG. *Penicillium marneffei*: an insurgent species among the penicillia. *J Eukaryotic Microbiol* 2000; **47**: 24–8.
149. Kudeken N, Kawakami K, Kusano N, Saito A. Cell-mediated immunity in host resistance against infection caused by *Penicillium marneffei*. *J Med Vet Mycol* 1996; **34**: 371–8.
150. Kudeken N, Kawakami K, Saito A. Cytokine-induced fungicidal activity of human polymorphonuclear leukocytes against *Penicillium marneffei*. *FEMS Immunol Med Microbiol* 1999; **26**: 115–24.
151. Vanittanakom N, Cooper CR Jr, Chariyalertsak S, Youngchim S, Nelson KE, Sirisanthana T. Restriction endonuclease analysis of *Penicillium marneffei*. *J Clin Microbiol* 1996; **34**: 1834–6.
152. Chariyalertsak S, Sirisanthana T, Supparatpinyo K, Praparattanapan J, Nelson KE. Case-control study of risk factors for *Penicillium marneffei* infection in human immunodeficiency virus-infected patients in northern Thailand. *Clin Infectious Dis* 1997; **24**: 1080–6.
153. Boon-Long J, Mekha N, Poonwan N *et al. In vitro* antifungal activity of the new triazole D0870 against *Penicillium marneffei* compared with that of amphotericin B, fluconazole, itraconazole, miconazole and flucytosine. *Mycoses* 1996; **39**: 453–6.
154. Supparatpinyo K, Nelson KE, Merz WG *et al.* Response to antifungal therapy by human immunodeficiency virus-infected patients with disseminated *Penicillium marneffei* infections and *in vitro* susceptibilities of isolates from clinical specimens. *Antimicrobial Agents Chemotherapy* 1993; **37**: 2407–11.
155. Sirisanthana T, Supparatpinyo K, Perriens J, Nelson KE. Amphotericin B and itraconazole for treatment of disseminated *Penicillium marneffei* infection in human immunodeficiency virus-infected patients. *Clin Infectious Dis* 1998; **26**: 1107–10.
156. Supparatpinyo K, Perriens J, Nelson KE, Sirisanthana T. A controlled trial of itraconazole to prevent relapse of *Penicillium marneffei* infection in patients infected with the human immunodeficiency virus. *New England J Med* 1998; **339**: 1739–43.
157. Walsh TJ, Newman KR, Moody M, Wharton RC, Wade JC. Trichosporonosis in patients with neoplastic disease. *Medicine* 1986; **65**: 268–79.
158. Hoy J, Hsu K, Rolston K, Hopfer RL, Luna M, Bodey GP. *Trichosporon beigelii* infection: a review. *Rev Infectious Dis* 1986; **8**: 959–67.
159. Krcmery V Jr, Mateicka F, Kunova A *et al.* Hematogenous trichosporonosis in cancer patients: report of 12 cases including 5 during prophylaxis with itraconazole. *Supportive Care Cancer* 1999; **7**: 39–43.
160. Erer B, Galimberti M, Lucarelli G *et al. Trichosporon beigelii*: a life-threatening pathogen in immunocompromised hosts. *Bone Marrow Transplantation* 2000; **25**: 745–9.
161. Anaissie E, Gokoslan A, Hachem R, Rubin R. Azole therapy for trichosporonosis: clinical evaluation of eight patients, experimental therapy for murine infection, and review. *Clin Infectious Dis* 1992; **15**: 781–7.
162. Lee JW, Melcher GA, Rinaldi MG, Andrews J, Pizzo PA, Walsh TJ. Patterns of morphologic variation in strains of *Trichosporon beigelii*. *J Clin Microbiol* 1990; **28**: 2823–7.
163. Kemeker BJ, Lehman PF, Lee JW, Walsh TJ. Distinction of deep vs. superficial clinical and non-clinical environmental isolates of *Trichosporon beigelii* by isoenzymes and RFLP's of rDNA generated by the polymerase chain reaction. *Antimicrobial Agents Chemotherapy* 1991; **29**: 1677–83.
164. Gueho E, Smith MT, de Hoog GS, Billon-Grand G, Christen R, Batenburg-van der Vegte WH. Contributions to a revision of the genus Trichosporon. *Antonie Van Leeuwenhoek* 1992; **61**: 289–316.
165. Walsh TJ, Melcher GP, Lee JW, Pizzo PA. Infections due to *Trichosporon* species: new concepts in mycology, pathogenesis, diagnosis, and treatment. *Current Topics Med Mycol* 1993; **5**: 79–113.

166. Walsh TJ, Melcher G, Rinaldi M *et al. Trichosporon beigelii*: an emerging pathogen resistant to amphotericin B. *J Clin Microbiol* 1990; **28**: 1616–22.
167. McManus EJ, Jones JM. Detection of a *Trichosporon beigelii* antigen cross-reactive with *Cryptococcus neoformans* capsular polysaccharide in serum from a patient with disseminated *Trichosporon* infection. *J Clin Microbiol* 1985; **21**: 681.
168. Melcher GA, Reed KD, Rinaldi MG, Lee JW, Pizzo PA, Walsh TJ. Demonstration of a cell wall antigen cross-reacting with cryptococcal polysaccharide in experimental disseminated trichosporonosis. *J Clin Microbiol* 1991; **29**: 192–6.
169. Lyman CA, Devi S, Nathanson J, Frasch CE, Pizzo PA, Walsh TJ. Detection and quantification of the glucuronoxylomannan-like polysaccharide antigen from clinical and non-clinical isolates of *Trichosporon beigelii:* implications for pathogenicity. *J Clin Microbiol* 1994; **33**: 126–30.
170. Lyman CA, Garrett KF, Pizzo PA, Walsh TJ. Response of human polymorphonuclear leukocytes and monocytes to *Trichosporon beigelii*: host defense against an emerging pathogen. *J Infectious Dis* 1994; **170**: 1557–65.
171. Walsh TJ, Lee JW, Melcher GP *et al.* Experimental disseminated trichosporonosis in persistently granulocytopenic rabbits: implications for pathogenesis, diagnosis, and treatment of an emerging opportunistic infection. *J Infectious Dis* 1992; **166**: 121–33.
172. Lopez-Berestein G, Mehta R, Hopfer RL *et al.* Treatment and prophylaxis of disseminated infection due to *Candida albicans* in mice with liposome-encapsulated amphotericin B. *J Infectious Dis* 1983; **147**: 939–45.
173. Melez KA, Cherry J, Sanchez C, Ettinger RB, Walsh TJ. Successful outpatient treatment of *Trichosporon beigelii* peritonitis with oral fluconazole. *Pediatric Infectious Dis J* 1995; **14**: 1110–3.
174. Martino P, Venditti M, Micozzi A *et al. Blastoschizomyces capitatus*: an emerging cause of invasive fungal disease in leukemia patients. *Rev Infectious Dis* 1990; **12**: 570–82.
175. Sanz MA, Lopez F, Martinez ML *et al.* Disseminated Blastoschizomyces capitatus infection in acute myeloblastic leukaemia. Report of three cases. *Supportive Care Cancer* 1996; **4**: 291–3.
176. Krcmery V, Krupova I, Denning DW. Invasive yeast infections other than *Candida* spp. in acute leukaemia. *J Hospital Infection* 1999; **41**: 181–94.
177. Perez-Sanchez I, Anguita J, Martin-Rabadan P *et al. Blastoschizomyces capitatus* infection in acute leukemia patients. *Leukemia Lymphoma* 2000; **39**: 209–12.
178. Venditti M, Posteraro B, Morace G, Martino P. *In-vitro* comparative activity of fluconazole and other antifungal agents against *Blastoschizomyces capitatus*. *J Chemotherapy* 1991; **3**: 13–5.
179. D'Antonio D, Mazzoni A, Iacone A *et al.* Emergence of fluconazole-resistant strains of *Blastoschizomyces capitatus* causing nosocomial infections in cancer patients. *J Clin Microbiol* 1996; **34**: 753–5.
180. Pagano L, Morace G, Ortu-La Barbera E, Sanguinetti M, Leone G. Adjuvant therapy with rhGM-CSF for the treatment of *Blastoschizomyces capitatus* systemic infection in a patient with acute myeloid leukemia. *Ann Hematol* 1996; **73**: 33–4.
181. Klotz SA. *Malassezia furfur. Infectious Dis Clin North Am* 1989; **3**: 53–64.
182. Marcon MJ, Powell DA. Human infections due to *Malassezia* spp. *Clin Microbiol Rev* 1992; **5**: 101–19.
183. Barber GR, Brown AE, Kiehn TE, Edwards FF, Armstrong D. Catheter-related *Malassezia furfur* fungemia in immunocompromised patients. *Am J Med* 1993; **95**: 365–70.
184. Morrison VA, Weisdorf DJ. The spectrum of *Malassezia* infections in the bone marrow transplant population. *Bone Marrow Transplant* 2000; **26**: 645–8.
185. Redline RW, Redline SS, Boxerbaum B, Dahms BB. Systemic *Malassezia furfur* infections in patients receiving intralipid therapy. *Human Pathol* 1985; **16**: 815–22.
186. Dankner WM, Spector SA, Fierer J, Davis CE. Malassezia fungemia in neonates and adults: complication of hyperalimentation. *Rev Infectious Dis* 1987; **9**: 743–53.
187. Chang HJ, Miller HL, Watkins N *et al.* An epidemic of *Malassezia pachydermatis* in an intensive care nursery associated with colonization of health care workers' pet dogs. *New Engl J Med* 1998; **338**: 706–11.
188. Sandin RL, Fang TT, Hiemenz JW *et al.* Malassezia furfur folliculitis in cancer patients. The need for interaction ofmicrobiologist, surgical pathologist, and clinician in facilitating identification by the clinical microbiology laboratory. *Ann Clin Laboratory Sci* 1993; **23**: 377–84.
189. Gupta AK, Kohli Y, Li A, Faergemann J, Summerbell RC. In vitro susceptibility of the seven *Malassezia* species to ketoconazole, voriconazole, itraconazole and terbinafine. *Br J Dermatol* 2000; **142**: 758–65.
190. Haron E, Anaissie E, Dumphy F, McCredie K, Fainstein V. *Hansenula anomala* fungemia. *Rev Infectious Dis* 1988; **10**: 1182–6.
191. Munoz P, Garcia Leoni ME, Berenguer J, Bernaldo de Quiros JC, Bouza E. Catheter-related fungemia by *Hansenula anomala. Arch Intern Med* 1989; **149**: 709–13.
192. Braun DK, Kauffman CA. Rhodotorula fungaemia: a life-threatening complication of indwelling central venous catheters. *Mycoses* 1992; **35**: 305–8.
193. Hazen KC. New and emerging yeast pathogens. *Clin Microbiol Rev* 1995; **8**: 462–78.
194. Johnson LB, Bradley SF, Kauffman CA. Fungaemia due to *Cryptococcus laurentii* and a review of non-neoformans cryptococcaemia. *Mycoses* 1998; **41**: 277–80.
195. Aucott JN, Fayen J, Grossnicklas H, Morrissey A, Lederman MM, Salata RA. Invasive infection with *Saccharomyces cerevisiae*: report of three cases and review. *Rev Infectious Dis* 1990; **12**: 406–11.
196. Kiehn TE, Gorey E, Brown AE, Edwards FF, Armstrong D. Sepsis due to Rhodotorula related to use of indwelling central venous catheters. *Clin Infectious Dis* 1992; **14**: 841–6.
197. Klein AS, Tortora GT, Malowitz R, Greene WH. *Hansenula anomala*: a new fungal pathogen. Two case reports and a review of the literature. *Arch Intern Med* 1988; **148**: 1210–3.
198. Pfaller MA, Messer S, Jones RN. Activity of a new triazole, Sch 56592, compared with those of four other antifungal agents tested against clinical isolates of *Candida* spp. & *Saccharomyces cerevisiae. Antimicrobial Agents Chemotherapy* 1997; **41**: 233–5.
199. Barchiesi F, Arzeni D, Compagnucci P, Di Francesco LF, Giacometti A, Scalise G. *In vitro* activity of five antifungal agents against clinical isolates of *Saccharomyces cerevisiae. Med Mycol* 1998; **36**: 437–40.
200. Barchiesi F, Arzeni D, Fothergill AW *et al.* In vitro activities of the new antifungal triazole SCH 56592 against common and emerging yeast pathogens. *Antimicrobial Agents Chemotherapy* 2000; **44**: 226–9.
201. Hiemenz JW, Walsh TJ. Lipid formulations of amphotericin B. recent progress and future directions. *Clin Infectious Dis* 1996; **22 (Suppl. 2)**: S133–S144.
202. Wong-Beringer A, Jacobs RA, Guglielmo BJ. Lipid formulations of amphotericin B. clinical efficacy and toxicities. *Clin Infectious Dis* 1998; **27**: 603–18.
203. Groll AH, Lucca AJ, Walsh TJ. Emerging targets for novel antifungal therapeutics. *Trends Microbiol* 1998; **6**: 117–24.
204. Groll AH, Walsh TJ. Potential new antifungal agents. *Current Opinion Infectious Dis* 1997; **10**: 449–58.
205. Kurtz MB, Douglas CM. Lipopeptide inhibitors of fungal glucan synthase. *J Med Vet Mycol*1997; **35**: 79–86.
206. Roilides E, Dignani MC, Anaissie EJ, Rex JH. The role of immunoreconstitution in the management of refractory opportunistic fungal infections. *Med Mycol* 1998; **36 (Suppl. 1)**: 12–25.